INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2004; **19**: 575–581.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1134

Critical Flicker Fusion Threshold in patients with Alzheimer's disease and vascular dementia

Stephen Curran[1]*, Simon Wilson[2], Shabir Musa[3] and John Wattis[1]

[1]*Ageing and Mental Health Research Group, School of Human and Health Sciences, University of Huddersfield, and Consultant in Old Age Psychiatry, South West Yorkshire Mental Health NHS Trust, Wakefield, UK*
[2]*Consultant in Old Age Psychiatry, Northumbria Healthcare NHS Trust, Ash Court, North Tyneside General Hospital, North Shields, Tyne and Wear, UK*
[3]*Consultant in Old Age Psychiatry, South West Yorkshire Mental Health NHS Trust, Fieldhead, Wakefield, UK*

SUMMARY

Background Critical Flicker Fusion Threshold (CFFT) is a psychophysical threshold and in psychological terms is regarded as a measure of information processing capacity. The test has previously been shown to be a valid and reliable measure of CNS functioning in patients with Alzheimer's disease and may be a useful as a screening measure for the early detection of Alzheimer's disease (AD).
Methods Consecutive referrals to the Wakefield Memory Clinic who met DSM-IV criteria for AD or vascular dementia (VaD) were invited to take part in the study. A range of neuropsychological tests and CFFT were administered to the two groups using standardised protocols and the ability of these various tests to distinguish between the two conditions was investigated.
Results Forty-six patients were included in the study. Of the various tests, only the descending component of CFFT and word fluency were significantly different in the two groups. In addition, the descending threshold had a sensitivity of 83% and a specificity of 69%.
Conclusion CFFT could be useful as a screening instrument for early AD when combined with other measures and could facilitate the decision to commence antidementia treatment at an early stage. Further longitudinal work is needed to establish this.

KEY WORDS — Alzheimer's disease; vascular dementia; early detection; critical flicker fusion

INTRODUCTION

In Alzheimer's disease (AD), and other forms of dementia, brain damage occurs before clinical symptoms become apparent. Drugs for the treatment of AD are now available and the sooner such drugs can be given the greater the potential clinical benefit. This has led to a drive to try and detect AD early, ideally before memory disturbance appears. There is a need for a non-invasive, easy to use and inexpensive means of *screening* people at risk of developing AD to help facilitate the decision to commence treatment.

*Correspondence to: Professor S. Curran, Ageing and Mental Health Research Group, HW3-02, Harold Wilson Building, School of Human and Health Sciences, University of Huddersfield, HD1 3DH, UK. Tel: 01924 328693. E-mail: s.curran@hud.ac.uk

IDENTIFYING EARLY ALZHEIMER'S DISEASE

There are a variety of techniques that can assist in the early detection of pre-clinical or early AD. Neuroimaging techniques will show alterations in brain structure (Frisoni *et al.*, 2002) or function (Salmon, 2002). However, there is considerable overlap with healthy older people and these procedures are expensive and cumbersome to use on a large scale. Various biochemical tests, e.g. mitogen-activated protein kinase dysfunction (Zhao *et al.*, 2002) and a variety of cerebro-spinal fluid (CSF) markers have been evaluated with promising results. However, lumbar puncture is invasive, uncomfortable, time consuming and potentially harmful. There have also been exciting developments in molecular medicine and the molecular basis of AD is becoming clearer (Rogaeva *et al.*,

Received 29 September 2003
Accepted 3 March 2004

2001). Although genetic screening may indicate who is at risk of developing AD, it gives no indication about *when* an individual is likely to develop the condition. Cognitive testing for early dementia is another possibility (Assal and Cummings, 2002) but, by definition, if cognitive changes are present, AD is already clinically apparent and the ideal point for intervention may already have passed. More recently, olfactory dysfunction has been suggested as a possible means of identifying early AD but more work is needed and there is no standardised test (Lange *et al.*, 2002). Many of these tests have potential as diagnostic tests but neuroimaging techniques and tests requiring a CSF sample are poorly suited for use as screening instruments.

CRITICAL FLICKER FUSION THRESHOLD (CFFT)

Critical Flicker Fusion Threshold (CFFT) is a well established psychometric measure which has been extensively studied in young and older healthy volunteers and is a measure of the ability of the Central Nervous System (CNS) to perceive flickering light, and the neurophysiological basis of flicker perception is well described (Curran and Wattis, 2000). Flickering light directly influences cortical activity (as measured by EEG). Walker *et al.* (1944) examined the different components of the visual system and demonstrated that the EEG activity recorded over the occipital cortex was synchronous with the frequency of retinal stimulation. The central (CNS) nature of flicker perception is also supported by other evidence including higher values when measured with binocular vision compared with monocular vision (Ali and Amir, 1991) and the CFFT is also increased by CNS stimulants and decreased by CNS depressants (Davranche and Audiffren, 2002). Although flickering light is able to initiate neuronal activity in various parts of the visual system (from retina to cortex), the temporal resolution of CFFT is determined principally by the occipital cortex.

A number of studies in the late 1940s reported reductions in CFFT in patients with cortical lesions including the occipital and frontal lobes (Landis, 1949). Simonson and Brozek (1952), in an extensive review of the factors influencing CFFT, reported reductions in CFFT scores in patients with tumours affecting the optic nerve, chiasma, the corpus callosum and frontal, temporal and parietal cortices. As the visual association cortex is extensively connected with other cortical association areas as well as with subcortical nuclei (Barr, 1979), this may explain why damage in various cortical areas influences the CFFT even though flicker is initially processed in the occipital cortex.

Recently, histological examination of the optic nerve in patients with AD has revealed selective degeneration and demyelination of long axons from the retina (Kurylo *et al.*, 1994). Since it is known that there is a point-to-point representation of retinal neurons in the occipital cortex, one may predict that CFFT scores would be affected in these patients. Furthermore, in demyelination, the speed of conduction of nerve impulses is markedly lowered, a deficit that would result in a reduced cortical input during a defined time interval; this may be one explanation for the reduced CFFT. For these reasons it was felt that there was sufficient evidence to investigate the behaviour of CFFT further in patients with AD.

In the ascending mode, the frequency of flicker is gradually increased until the lights no longer appear to flicker (ascending threshold). In the descending mode, the frequency of flicker is gradually decreased until the lights appear to start flickering (descending threshold). The CFFT is the average of the ascending and descending thresholds.

CFFT scores measured in 644 healthy community based older people were normally distributed and descending thresholds were significantly higher than ascending thresholds confirming findings from studies in younger subjects. There were no significant correlations between CFFT, ascending and descending thresholds and age but there was a non-significant negative correlation between age and descending thresholds. The lack of a correlation between CFFT, ascending and descending thresholds and age is important since if CFFT scores were correlated with age, the test would be unable to distinguish between change in cognitive function due to age or disease (Curran *et al.*, 1990).

CFFT, ascending and descending thresholds have also been examined in patients with AD and healthy controls. CFFT and descending thresholds were significantly lower in patients with AD compared with normal controls whereas ascending thresholds were not significantly different in the two groups. The finding that descending scores were significantly lower than ascending scores is the opposite of the finding in normal healthy subjects. This reversal may be a characteristic feature of patients with AD (Curran *et al.*, 1991a). In a series of further studies in patients with AD, CFFT has also been shown to have a high test–retest reliability (Curran *et al.*, 1991b), high inter-rater reliability (Curran *et al.*, 1994) and to be a valid measure in patients with AD (Curran *et al.*, 1992).

This study examined the ability of CFFT and its subcomponents (ascending and descending thresholds) to distinguish between patients with AD and VaD and compared these with a range of psychometric and neuropsychological measures. AD and VaD are both common and there is considerable overlap between them, e.g. clinical symptoms and cardiovascular risk factors. Distinguishing between these two conditions is important since treatments for AD could be more focused and started sooner thus increasing the chances of therapeutic benefits. It would also be important for CFFT to be able to distinguish AD from other conditions including other degenerative dementias and depressive pseudodementia but the focus of this study is VaD.

METHODOLOGY

Patients

All patients included in the study were referred to the Wakefield Memory Clinic, UK either by geriatricians or general practioners and most patients had had a detailed physical assessment before referral. Consecutive referrals were assessed and if they met DSM-IV (APA, 1994) diagnostic criteria for AD or vascular dementia (VaD) they were invited to take part in the study. The ischaemic score (Hachinski, 1978) was also used to facilitate diagnosis. Assessments in the clinic included a psychiatric history and mental state examination, physical examination, routine laboratory investigations and a CT scan and a nursing assessment The radiologist had a specific interest in neuroradiology. Additional information was also obtained from the main carer and the general practioner. Additional investigations, e.g. ECGs and CXRs were only undertaken if clinically indicated. Patients and the main carer received an information sheet about the study and, after an opportunity to discuss this with their family, gave their written consent. This was also obtained from a family member and the study was approved by the Wakefield Research Ethics Committee.

Materials

For all tests standardised instructions were used and the tester was blind to the patient's diagnosis. CFFT was measured using the Leeds Psychomotor Tester (Frewer and Hindmarch, 1988). The equipment is portable and simple to use. When open, the central part of a raised section has four red lights which flicker with variable frequency. A push button used by the subject to stop recording, is permanently attached to the investigator's console and is on a 1 m lead. CFFT was measured using four red light-emitting diodes in binocular foveal fixation. The continuous psychophysical method of limits was employed (Woodworth and Schlosberg, 1958). The lights were at eye level, and ambient illumination was diffuse without shadow or bright sunlight. When this obtains, ambient illumination has very little effect on the CFFT (Simonson and Brozek, 1952). In the *ascending mode*, flicker was increased from 12 Hz at 1 Hz/s. The subject was required to press a button when flickering appeared to cease (ascending threshold). In the *descending mode*, flicker was decreased from 50 Hz at 1 Hz/s until flicker was just detected and registered by a button press (descending threshold). The starting points of 50 Hz and 12 Hz were default settings and were varied by the investigator to prevent subjects pressing the button press after a given time, and thus always seeming to get the same result (*error of anticipation*). Prior to testing, the subject was familiarised with the machine. The CFFT was the average of three ascending and three descending scores.

In addition to CFFT, the following were administered:

Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975). The MMSE is a short, standardised mental status examination, used to estimate severity of cognitive impairment. It assesses orientation in time and place, instantaneous recall, short-term memory, abilities to perform a series of subtractions or reverse spelling, constructional abilities and the use of language. The MMSE score is produced by summing the points assigned to each successfully completed task and the maximum score is 30; lower scores are indicative of cognitive impairment. The test is not timed but usually requires no more than 5–10 minutes. A set of questions was provided on the test forms to standardise the administration of the scale.

Digit Span (Wechsler, 1955). This is a simple and popular two-part test of immediate memory from the Wechsler Adult Intelligence Scale (WAIS). In 'digits forward', patients are requested to repeat the digits in the order presented and in 'digits backward', patients repeat the digits in reverse order. 'Digits forward and backward' are both sensitive to left-hemisphere damage (Lezak, 1983) and both have been shown to be reduced in patients with AD. (Lezak, 1983) 'Digits forward' and 'digits backward' were combined to produce 'digits total'.

Digits forward: The subject had to repeat each number sequence, range 3–9, exactly as it was given. When the sequence was repeated correctly (two trials on each sequence were allowed), the next longer sequence was given to the patient and this was continued until the patient failed a pair of sequences or all sequences were correctly repeated.

Digits backward: The digits backward number sequences ranged from 2–8 in length. On hearing them the patient's task was to say them in reverse order. The test continued until the patient failed a pair of sequences (two trials on each sequence were allowed) or recalled eight reversed digits correctly. Again, the patient was allowed two trials on each sequence.

Trail Making Test (TMT) (Reitan, 1958). This test is thought to provide a measure of visuo-motor tracking and the 'general speed of cognitive performance'. It is one of the most sensitive measures of brain damage. The inter-rater reliability has been reported to be between 0.67–0.78 (Lezak, 1983). The TMT consists of 25 circles numbered 1 through to 25 on a white piece of paper (test sheet). Patients were instructed to connect the circles, in numerical order, as rapidly as possible. Patients were given a maximum of three minutes to complete the task. The test was preceded by an eight item practice test and the final measure is the time taken to complete the task. If a circle was connected out of order, the patient was stopped, the error pointed out and corrected, and the patient continued with the test. In instances where the patient did not complete the test in the allotted time, the number of correctly connected circles was recorded.

Digit Symbol Substitution Test (DSST) (Wechsler, 1955). The DSST is also a subtest of the WAIS and measures aspects of learning ability, immediate retention and psychomotor performance (Erber *et al.*, 1981). However, other skills involved include attention/concentration, response speed and visuo-motor co-ordination (Lezak, 1983). It is very sensitive to right hemisphere damage, particularly right frontal damage. Such patients are prone to make orientation errors, especially reversal mistakes. This test has consistently been shown to be more sensitive to brain damage than other WAIS battery subtests, and scores are likely to be affected when brain damage is minimal (Lezak, 1983). It has also been used in the assessment of patients with brain damage, including patients with AD (Lezak, 1983).

Word Fluency (WF) (Benton, 1968). Word Fluency tests both mental speed and organisation with regard to semantic memory and has been found to be a sensitive indicator of brain dysfunction, especially frontal lobe damage. It has also been widely used and shown to be impaired in patients with AD (Miller and Morris, 1993). Patients were given a letter of the alphabet, and asked to say as many words as possible beginning with that letter. Proper names, names of places or different forms of the same word were excluded. A practice trial was carried out before testing began. The practice trial used the very high frequency letter 's' and terminated when two correct responses had been given. The patient was then given a new letter, and asked to say as many words as possible beginning with that letter. The patient was allowed one minute to complete the task. If the patient discontinued before the end of the trial, he/she was encouraged to try and find more words and all responses were recorded. If clarification was needed on a word by the investigator, this was done at the end of the trial period.

Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964). The RAVLT is an easily administered test of immediate memory span. It provides a measure of learning and is sensitive to both confusion and confabulation and has been shown to be impaired in patients with brain damage, particularly of the left hemisphere compared with controls (Lezak, 1983). It consists of five presentations of a list containing ten semantically unrelated words which should be recalled by the subject after every presentation. The total number of words correctly recalled was recorded, all summed over the five trials. This instrument took approximately ten minutes to administer.

Choice Reaction Time (CRT) (Hindmarch *et al.*, 1988). CRT is a widely used psychometric instrument with an extensive body of literature. Hindmarch and Wattis (1988) have suggested that CRT is an indicator of sensori-motor performance. It has also been proposed as a measure of the efficiency of attentional and response mechanisms in the information-processing chain, without the need for extensive cognitive processing (Sherwood, 1994). From the central starting position (start pad), patients were required on each trial, to extinguish one of six lights, illuminated at random, by touching the appropriate adjacent response button which were touch sensitive. These light/button combinations were arranged in a 120 degree arc, with 24 degrees between each, on a 15 cm radius circle centred on and forward of the start button. The hand was held clenched, with the index finger of the dominant (or preferred) hand extended.

The total time elapsed between the stimulus light appearing, and the appropriate button being pressed, is the total reaction time (TRT) and this was recorded automatically. The time taken for the finger to move off the central pad is the recognition reaction time (RRT). The difference between these (TRT-RRT) is the motor reaction time (MRT). Prior to formal testing, subjects were fully familiarised with the test procedure. Following this, a trial of 50 presentations was carried out and this constituted the practice phase. In the experimental phase, a further 50 scores were determined and the mean of these was recorded.

RESULTS

Forty-six patients were included in the study and patient characteristics are summarised in Table 1. Of these, 30 had a diagnosis of AD and 16 VaD. The two groups were not significantly different in terms of cognitive impairment as measured by the MMSE (Mann–Whitney $U = 212$, $p < 0.52$).

CFFT, CRT and their subcomponents were compared in patients with AD and VaD using Student's *t*-tests (continuous data). The remaining psychometric measures were compared using the Mann–Whitney-U test for independent samples (ordinal data). These results are summarised in Tables 2 and 3. Most of the measures were not able to distinguish between AD and VaD with the exception of word fluency (which just reached significance) and the descending scores of the CFFT test.

Table 1. Summary of patient characteristics

Diagnosis	Mean age in years	Standard deviation (age)	MMSE (mean scores)
VaD	75.5	6.4	19.2
AD	75.8	6.0	20.0

Table 2. Comparison of ascending (ASD) and descending (DES) thresholds, critical flicker fusion threshold (CFFT), Total Reaction Time (TRT), Recognition Reaction Time (RRT) and Motor Reaction Time (MRT) in patients with Alzheimer's disease (AD) and vascular dementia (VaD) using students *t*-test (*significant result)

Diagnosis	Test	N	Mean	SD	Significance
VaD	ASD	16	24.3 Hz	4.8	0.61
AD		30	25 Hz	3.7	
VaD	DES	16	25.4 Hz	4.5	0.018*
AD		30	22.6 Hz	3.2	
VaD	CFFT	16	24.9 Hz	4.3	0.30
AD		30	23.8 Hz	2.7	
VaD	TRT	13	1651 ms	1247	0.42
AD		28	2157 ms	2049	
VaD	RRT	13	993 ms	893	0.58
AD		28	1212 ms	1256	
VaD	MRT	13	658 ms	751	0.58
AD		28	872 ms	1275	

VaD = vascular dementia; AD = Alzheimer's dementia.

Table 3. Comparison of total digits (TD), Trail Making Test (TMT), Digit Symbol Substitution Test (DSST), and Rey Auditory Verbal Learning Test (RAVLT) in patients with Alzheimer's disease (AD) and vascular dementia (VaD) using the Mann–Whitney U-test (*significant result)

Diagnosis	Test	N	Mean rank	Significance
VaD	TD	15	18.8	0.28
AD		27	23	
VaD	TMT	15	21.5	0.84
AD		26	20.7	
VaD	DSST	12	21.4	0.62
AD		27	19.4	
VaD	WF	14	15.8	0.045*
AD		27	23.7	
VaD	RAVLT	14	20.4	0.81
AD		27	21.3	

VaD = vascular dementia; AD = Alzheimer's dementia.

Table 4. Comparison of the proportion of reversals (descending scores lower than ascending scores) in patients with Alzheimer's disease (AD) and vascular dementia (VaD)

Diagnosis	Reversal (YES)	Reversal (NO)
AD	24	5
VaD	5	11

$\chi^2 = 11.9$, df = 1, $p < 0.001$.

In healthy younger and older people, the descending scores are greater than ascending scores. In this study, a greater proportion of patients with AD showed a reversal (descending scores lower than ascending scores) compared with patients with VaD ($\chi^2 = 11.9$, $p < 0.001$) and this is summarised in Table 4. In addition, the descending scores had a sensitivity of 83% and a specificity of 69%.

CONCLUSIONS

CFFT has been widely used over the past 30–40 years to investigate the effects of psychoactive drugs and in young and older healthy volunteers and it has been shown to correlate with a range of CNS measures. It also satisfies many of the features of an 'ideal' assessment instrument. The test is not influenced by cultural or educational factors and it is also economic as well as being quick and easy to administer. In addition, the test is not affected by floor or ceiling effects and it can

be easily administered by staff with relatively little training. Consequently, it is now one of the most popular techniques in psychometric research.

CFFT can be measured in a number of different ways. One method (*the Method of Limits*) involves increasing the frequency of a light source until the flickering appears to stop. The point at which this occurs is the ascending threshold. The frequency of the same flickering light is then reduced from a high level until flickering appears to start and this point is the descending threshold. The average of the ascending and descending threshold is the CFFT.

In healthy older subjects, CFFT scores are normally distributed and do not change significantly over the age range 60–90 years. The latter point is important since a measure that is sensitive to change in cognitive function due to increasing age and worsening pathology (e.g. AD) would be very difficult to interpret, especially during the early stages of the disease. Previous work has shown that CFFT is significantly impaired in patients with AD compared with controls and the test has been shown to be a reliable and valid measure of CNS function in this patient group. In addition, in healthy older subjects, descending thresholds are consistently higher than ascending thresholds and this may be due to low and high frequency flicker being processed by different neuronal pathways. Interestingly, patients with AD have significantly lower descending thresholds and this might be a characteristic feature of AD. One explanation may be that the disease process in AD differentially affects the two neuronal pathways for flicker detection.

The two groups were not significantly different in terms of their level of global cognitive impairment as measured using the MMSE VaD = 19.2 and AD = 20.0) and their ages were also not significantly different (VaD = 75.5 years and AD = 75.8 years). However, there is no gold standard for the diagnosis of AD and VaD and there is good evidence now that there is considerable overlap between these two conditions. Vascular changes can increase the risk of AD and there is considerable overlap between the two conditions in relation to vascular risk factors. Small white matter changes are also frequently missed on CT scans. There is a growing consensus that the whole area and particularly the classification and diagnosis needs to be re-examined. It is therefore very likely that the groups studied did not represent 'pure' VaD and AD pathology and there was almost certainly some overlap between these groups. This will make interpretation of results more difficult and will reduce the sensitivity and specificity of a particular test because of the clinical heterogeneity.

In this study, most of the measures were not significantly different in patients with AD and VaD. However, word fluency scores were significantly lower in patients with VaD and descending thresholds in patients with AD. Language function is known to be relatively well preserved in early AD whereas language function can be, and commonly is, impaired in patients with mild to moderate VaD. In addition, descending thresholds are known to be decreased in patients in AD and if this is not a feature of VaD this would be an explanation for this difference. The overlap that is observed is possibly due to some patients having a mixed (VaD/AD) clinical syndrome. In addition, if the neuronal pathways for flicker perception are always affected in AD but only occasionally in VaD (e.g. due to 'random infarcts') it is likely that a significant difference would be seen. Furthermore, patients with AD were significantly more likely to have a *reversal*, i.e. in individual patients with AD the descending scores were lower than the ascending scores. In addition, the sensitivity and specificity of the descending scores were 83% and 69% respectively. These are relatively high considering that the majority of patients had mild impairment and the likelihood that an unknown proportion of the patients had a mixed clinical picture.

In a longitudinal context, descending thresholds may be helpful in identifying early cases of AD as part of the screening process. In addition, the test

KEY POINTS

- There is considerable overlap between vascular dementia and Alzheimer's disease and further research is needed to improve the classification and diagnostic criteria.
- Treatments for Alzheimer's disease have a better chance of working if these are given early. There is therefore a pressing need for a quick and easy to use instrument for screening purposes that can possibly detect Alzheimer's disease at an early or preferably preclinical stage.
- Critical flicker fusion is quick and easy to use and has a number of advantages over neuroimaging, tests requiring lumbar puncture and cognitive screening measures.
- In this study CFFT was able to distinguish between patients with vascular dementia and Alzheimer's disease and, with further research, has the potential to be a useful screening instrument.

requires minimal training and is relatively quick and easy to administer. It could also be used to monitor on a more regular basis patients at high risk of developing AD. When combined with clinical and other information it may help to inform the decision to commence patients on an antidementia drug at an early or possibly preclinical stage to help maximise any potential clinical benefits.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Chris Leach, Research Consultant, South West Yorkshire Mental Health NHS Trust, Fieldhead, Wakefield, WF1 3SP for his helpful comments and statistical advice.

REFERENCES

Ali MR, Amir T. 1991. Critical flicker frequency under monocular and binocular conditions. *Perceptual Motor Skills* **72**(2): 383–386.

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. APA: Washington, DC.

Assal F, Cummings JL. 2002. Neuropsychiatric symptoms in the dementias. *Curr Opin Neurol* **15**(4): 445–450.

Barr ML. 1979. *The Human Nervous System: An Anatomical Viewpoint*, 3rd edn. Harper International: Maryland, MD; 236–248.

Benton AL. 1968. Differential behavioural effects in frontal lobe disease. *Neuropsychologia* **6**: 53–60.

Curran S, Wattis JP, Shillingford C, Hindmarch I. 1990. Critical flicker fusion in normal elderly subjects: a cross-sectional community study (I). *Curr Psychol Res Rev* **9**(1): 25–34.

Curran S, Wattis JP, Shillingford C, Hindmarch I. 1991a. Critical Flicker Fusion in Primary Degenerative Dementia of the Alzheimer's Type (PDDAT): Clinical Implications (II). *Curr Psychol Res Rev* **9**(4): 397–406.

Curran S, Wattis JP, Hindmarch I. 1991b. Reliability of flicker threshold measurement in patients with Primary Degenerative Dementia of the Alzheimer's type (PDDAT). *Int J Geriatr Psychiatry* **6**: 517–521.

Curran S, Wattis JP, Hindmarch I. 1992. Concurrent validity of critical flicker fusion in patients with Primary Degenerative Dementia of the Alzheimer type. *Int J Geriatr Psychiatry* **7**: 573–578.

Curran S, Seymour J, Wattis JP. 1994. Inter-Rater Reliability of Critical Flicker Fusion in Patients with Primary Degenerative Dementia of the Alzheimer Type (PDDAT). *Int J Meth Psychiatric Res* **4**: 55–57.

Curran S, Wattis JP. 2000. Critical flicker fusion threshold; a potentially useful measure for the early detection of Alzheimer's disease. *Hum Psychopharmacol* **15**(2): 103–112.

Davranche K, Audiffren M. 2002. Effects of a low dose of transdermal nicotine on information processing. *Nicotine Tobacco Research* **4**(3): 275–285.

Erber JT, Botwinick J, Storandt M. 1981. The impact of memory on age differences in Digit Symbol Substitution performance. *J Gerontol* **36**: 586–590.

Folstein MF, Folstein SE, McHugh PR. 1975. 'Mini-mental State'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* **12**: 189–198.

Frewer LJ, Hindmarch I. 1988. The effects of time of day, age and anxiety on a choice reaction task. In *Psychopharmacology and Reaction Time*, Hindmarch I, Aufdembrinke B, Ott H (eds). John Wiley and Sons: Chichester; 103–114.

Frisoni GB, Rossi R, Beltramello A. 2002. The radial width of the temporal horn in mild cognitive impairment. *J Neuroimaging* **12**(4): 351–354.

Hachinski V. 1978. Differentiation of Alzheimer's disease from multi-infarct dementia. In *Alzheimer's Disease: Senile Dementia and Related Disorders*, Katzman R, Terry RD, Bick KL (eds). Raven Press: New York.

Hindmarch I, Aufdembrinke B, Ott H. 1988. *Psychopharmacology and Reaction Time*. John Wiley and Sons: Chichester.

Hindmarch I, Wattis JP. 1988. Measuring effects of psychotropic drugs. In *Psychological Assessment of the Elderly*, Wattis JP, Hindmarch I (eds). Churchill Livingstone: Edinburgh; 180–197.

Kurylo DD, Corkin S, Dolan RP, Rizzo JF, 3rd, Parker SW, Growdon JH. 1994. Broad-band visual capacities are not selectively impaired in Alzheimer's disease. *Neurobiol Aging* **15**(3): 305–311.

Landis C. 1949. *Selective Partial Ablation of the Frontal Cortex*. Hoeber: New York; 492–496.

Lange R, Donathan CL, Hughes LF. 2002. Assessing olfactory abilities with the University of Pennsylvania smell identification test; a Rasch scaling approach. *J Alzheim Dis* **4**(2): 77–91.

Lezak MD. 1983. *Neuropsychological Assessment*, 2nd edn. Oxford University Press: New York.

Miller E, Morris R. 1993. *The Psychology of Dementia*. John Wiley and Sons: Chichester.

Reitan RM. 1958. Validity of the Trail Making Test as an indication of organic brain damage. *Perceptual Motor Skills* **8**: 271–276.

Rey A. 1964. L'examen clinique en psychologie. Presses Universitaires de France: Paris.

Rogaeva E, Tandon A, St George-Hyslop PH. 2001. Genetic markers in the diagnosis of Alzheimer's disease. *J Alzheim Dis* **3**(3): 293–304.

Salmon E. 2002. Functional brain imaging applications to differential diagnosis in the dementias. *Curr Opin Neurol* **15**(4): 439–444.

Sherwood N. 1994. *Effects of nicotine on human psychomotor performance*. PhD thesis, University of Leeds.

Simonson E, Brozek J. 1952. Flicker fusion frequency: background and applications. *Physiological Rev* **32**: 349–378.

Walker AE, Woolfe JI, Halstead WC, Case TJ. 1944. Photic driving. *Arch Neurol Psychiatry* **52**: 117–125.

Wechsler D. 1955. *Wechsler Adult Intelligence Scale, Manual*. Psychological Corporation: New York.

Woodworth RS, Schlosberg H. 1958. *Experimental Psychology*. Methuen: London.

Zhao WQ, Ravindranath L, Mohamed AS, *et al.* 2002. MAP kinase signaling cascade dysfunction specific to Alzheimer's disease in fibroblasts. *Neurobiologic Disord* **11**(1): 166–183.

